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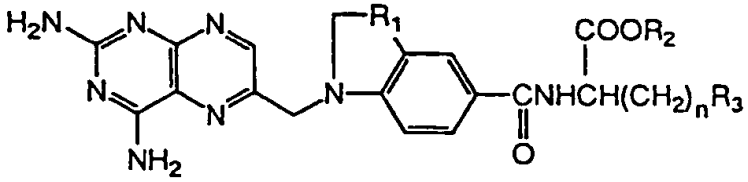
(54) UVEITIS REMEDY

(57) Remedies for uveitis which contain, as the active ingredient, one or more compounds represented by the following general formula (I) or salts thereof:



(I)

wherein R_1 represents a member selected from the group consisting of CH_2, CH_2CH_2, CH_2O, CH_2S and CH_2SO; R_2 represents a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms or a benzyl group; R_3 represents a group of the general formula $COOR_4$ (wherein R_4 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms), a group of the general formula $NHCOR_5$ (wherein R_5 represents an optionally substituted phenyl group), a group of the general formula $CONR_6R_7$ (wherein R_6 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; and R_7 represents a lower alkyl group having 1 to 4 carbon atoms, an optionally substituted phenyl group, a carboxyalkyl group or a lower alkylsulfonyl group), a PO_3H_2 group or an SO_3H group; and n is an integer of from 1 to 4.

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Description

TECHNICAL FIELD

[0001] This invention relates to drugs containing methotrexate derivatives. More particularly, it relates to drugs containing methotrexate derivatives which are efficacious against uveitis.

BACKGROUND ART

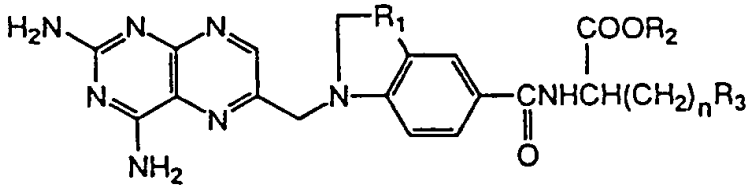
[0002] Although uveitis sometimes occurs in association with Behcet's disease, sarcoidosis, Harada's disease, etc., its pathogenesis is obscure in 50 to 70% of the patients. There are a number of findings on uveitis which can be classified into, for example, iridocyclitis (anterior uveitis), retinochoroiditis (posterior uveitis), panuveitis, intermediary uveitis, etc. depending on the inflammation site. To treat uveitis, steroids are commonly used, however, steroids occur side effects. Therefore, it has been urgently required to develop drugs efficacious against uveitis.

[0003] On the other hand, methotrexate (MTX), which is a folic acid metabolism antagonist, has been employed as a carcinostatic agent in treating acute leukemia, malignant lymphoma, etc. Also, MTX is known as an immunosuppressive agent and used mainly for preventing acute graft-versus-host reactions in bone marrow transplantation. Moreover, it is known that administration of MTX in a small dose is efficacious in treating rheumatoid arthritis.

DISCLOSURE OF THE INVENTION

[0004] It is an object of the present invention to provide excellent remedies for uveitis.

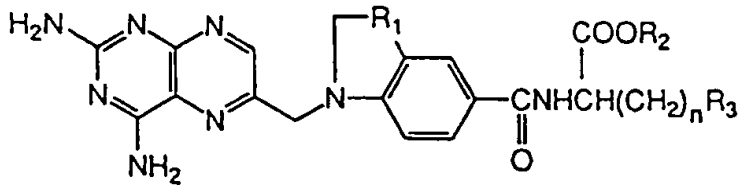
[0005] The present inventors have conducted extensive studies and consequently found that compounds represented by the following general formula (I) or salts thereof are useful as remedies for uveitis, thus completing the present invention:



(I)

wherein R_1 represents a member selected from the group consisting of CH_2, CH_2CH_2, CH_2O, CH_2S and CH_2SO; R_2 represents a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms or a benzyl group; R_3 represents a group of the general formula $COOR_4$ (wherein R_4 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms), a group of the general formula $NHCOR_5$ (wherein R_5 represents an optionally substituted phenyl group), a group of the general formula $CONR_6R_7$ (wherein R_6 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; and R_7 represents a lower alkyl group having 1 to 4 carbon atoms, an optionally substituted phenyl group, a carboxyalkyl group or a lower alkylsulfonyl group), a PO_3H_2group or an SO_3H group; and n is an integer of from 1 to 4.

[0006] Accordingly, the present invention relates to remedies for uveitis which contain, as the active ingredient, one or more compounds represented by the following general formula (I) or salts thereof:

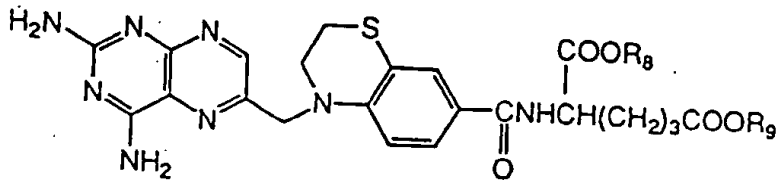


(I)

wherein R_1 represents a member selected from the group consisting of CH_2, CH_2CH_2, CH_2O, CH_2S and CH_2SO; R_2 represents a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms or a benzyl group; R_3 repre-

sents a group of the general formula $COOR_4$ (wherein R_4 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms), a group of the general formula $NHCOR_5$ (wherein R_5 represents an optionally substituted phenyl group), a group of the general formula $CONR_6R_7$ (wherein R_6 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; and R_7 represents a lower alkyl group having 1 to 4 carbon atoms, an optionally substituted phenyl group, a carboxyalkyl group or a lower alkylsulfonyl group), a PO_3H_2 group or an SO_3H group; and n is an integer of from 1 to 4.

[0007] The present invention further relates to remedies for uveitis which contain, as the active ingredient, one or more compounds represented by the following general formula (II) or salts thereof:



(II)

wherein R_8 and R_9 are the same or different and each represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms.

BRIEF DESCRIPTION OF THE DRAWING

[0008]

Fig. 1 is a graph which illustrates the effect of the drugs of the present invention on uveal retinitis.

BEST MODE FOR CARRYING OUT THE INVENTION

[0009] The compounds of the present invention represented by the general formula (I) are described in International Publication Gazette WO 92/03436 which provides data showing that these compounds inhibit the proliferation of human lymphocytes, rat and human keratinocytes and mouse cancer cells (P388, colon26). Based on these experimental data, it is suggested in this gazette that these compounds might be useful as remedies for rheumatoid arthritis, psoriasis and cancer. Moreover, International Publication Gazette WO 94/14810 presents data showing that the compounds represented by the general formula (II) inhibit the proliferation of synovial cells from rheumatoid arthritis patients, which suggests that these compounds are useful as antirheumatic agents.

[0010] However, it has never been reported so far that the compounds represented by the general formula (I) are efficacious against uveitis.

[0011] The drugs of the present invention are useful in treating uveitis. The term "uveitis" as used herein involves uveal retinitis, iridocyclitis (anterior uveitis), retinochoroiditis (posterior uveitis), panuveitis, intermediary uveitis, etc. Uveitis is roughly classified into endogenous uveitis and exogenous uveitis. Although the term "uveitis" as used herein involves both of the endogenous and exogenous ones, the drugs of the present invention are efficacious in particular for endogenous uveitis. Examples of the endogenous uveitis include those induced by Behcet's disease, sarcoidosis and Harada's disease, sympathetic ophthalmitis, etc.

[0012] The term "lower alkyl group" as used herein means linear or branched alkyl groups having 1 to 6 carbon atoms, unless the number of carbon atoms is otherwise specified. Preferable examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl groups. Examples of the lower alkyl group having 1 to 4 carbon atoms include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl groups.

[0013] Examples of the substituent in the optionally substituted phenyl group include lower alkyl, hydroxyl, amino, halogeno, cyano, lower alkyloxy, mercapto, acyl, acyloxy, phenyl, carboxyl and lower alkyloxycarbonyl groups. Among these substituents, carboxyl and lower alkyloxycarbonyl groups are preferable therefor.

[0014] The term "carboxyalkyl" group means lower alkyl groups substituted by one or more carboxyl groups. Preferable examples thereof are lower alkyl groups substituted by one carboxyl group. As a particularly preferable example thereof, a 3-carboxypropyl group may be cited.

[0015] As a preferable examples of the lower alkylsulfonyl group, a methanesulfonyl group may be cited.

[0016] The compounds of the present invention may be used in the form of their salts which are prepared by conventional methods. Examples of the salts usable in the present invention include inorganic acid salts such as hydrochloride, hydrobromide, hyrdoiodide, sulfate and phosphate; organic acid salts such as succinate, malonate, acetate, maleate,

fumarate, citrate, gluconate, mandelate, benzoate, salicylate, methanesulfonate, benzenesulfonate and p-toluenesulfonate; and metal salts such as sodium, potassium and magnesium salts. It is preferable to use inorganic acid salts or organic acid salts, still preferably hydrobromide or methanesulfonate, therefor.

[0017] Preferable examples of the compounds to be used in the remedies of the present invention include those described in International Publication Gazettes WO 92/03436 and WO 94/14810. Among all, the compound described in Example in International Publication Gazette WO 94/14810 may be cited as the most desirable one.

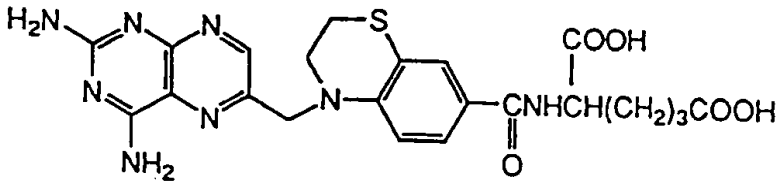
[0018] Although drugs containing the compounds of the present invention may be administered either orally or parenterally, oral administration is particularly preferred. The administration dose usually ranges from 0.01 to 100 mg/day/patient, though it may vary depending on, for example, the disease type and the body weight and conditions of the patient.

[0019] Examples of the dosage form of the drugs containing the compounds of the present invention are liquid preparations such as injections, tablets, capsules, dusts, etc.

[0020] Also, the drugs of the present invention can be locally administered as, for example, eye drops or injections. The local injection methods are exemplified by intraocular injection, subconjunctival injection and injection under Tenon's capsule.

Examples

[0021] To further illustrate the present invention in greater detail, the following examples will be given wherein N-(1-((2,4-diamino-6-pteridinyl)methyl)-3,4-dihydro-2H-1,4-benzothiazine-7-carbonyl)-L-α-aminoadipic acid of the following formula was employed as the compound of the present invention.



Example 1: Effect on rat experimental autoimmune uveal retinitis

[0022] Experimental autoimmune uveal retinitis was induced by immunizing Lewis rats with S antigen together with Freund's complete adjuvant. That is to say, S antigen (50 μg), which had been isolated from bovine retina in accordance with the method of Kozak et al. (Curr. Eye Res., Vol. 1, 327-337, 1981), was dissolved in PBS. Next, the obtained solution was mixed with the same amount of Freund's complete adjuvant (CFA) prepared by suspending Mycobacterium Tuberculosis H37Ra (10 mg/ml) in Freund's incomplete adjuvant (Difco) to give an emulsion. Female Lewis rats aged 8 weeks (Charles River) were immunized by subcutaneously injecting 0.1 ml/animal of this emulsion into the footpad. The severity of uveal retinitis was evaluated by observing the occurrence of intraocular inflammation with the naked eye and scored in 5 grades (0 to 4) as follows.

Score

[0023]

0 : normal.
1 : anterior uveitis, with all deposits in the pupil.
2 : total invasion of the pupil by the cellular infiltrate.
3 : severe inflammation associated with a corneal oedema.
4 : ocular proptosis, and haemorrhages in the anterior chamber.

[0024] The test compound was dissolved in PBS and then orally administered from the day of the immunization with S antigen (referred to as the day 0) 5 days per week for 3 weeks. The test compound was administered in a dose of 0.5 mg/kg/day or 2.5 mg/kg/day. On the other hand, PBS alone was administered to a control group. Each group had 3 ani-

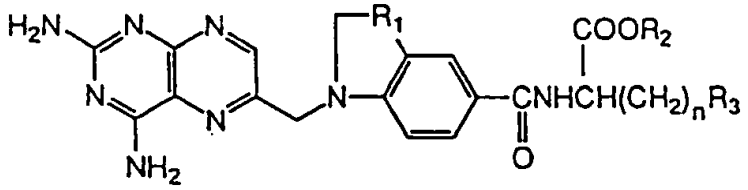
mals and the average score of each group was determined. Fig. 1 shows the results. In the control group, uveal retinitis broke out on the day 12 and the score reached to the maximum level (4) on the day 14. In the group with the administration of 0.5 mg/kg/day of the test compound, the onset of uveal retinitis was delayed. Namely, uveal retinitis broke out on the day 14 and the score reached to 4 on the day 19. In the group with the administration of 2.5 mg/kg/day of the test compound, the onset of uveal retinitis was completely inhibited. These facts indicate that the drugs of the present invention are useful as remedies for uveitis.

Industrial Applicability

[0025] As will be shown in the following examples, it has been confirmed that the drugs of the present invention are efficacious against experimental autoimmune uveal retinitis in rats. This fact suggests that the drugs of the present invention are useful as remedies for uveitis.

Claims

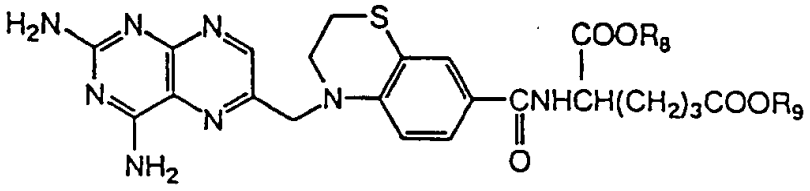
1. Remedies for uveitis which contain, as the active ingredient, one or more compounds represented by the following general formula (I) or salts thereof:



(I)

wherein R_1 represents a member selected from the group consisting of CH_2, CH_2CH_2, CH_2O, CH_2S and CH_2SO; R_2 represents a hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms or a benzyl group; R_3 represents a group of the general formula $COOR_4$ (wherein R_4 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms), a group of the general formula $NHCOR_5$ (wherein R_5 represents an optionally substituted phenyl group), a group of the general formula $CONR_6R_7$ (wherein R_6 represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; and R_7 represents a lower alkyl group having 1 to 4 carbon atoms, an optionally substituted phenyl group, a carboxyalkyl group or a lower alkylsulfonyl group), a PO_3H_2 group or an SO_3H group; and n is an integer of from 1 to 4.

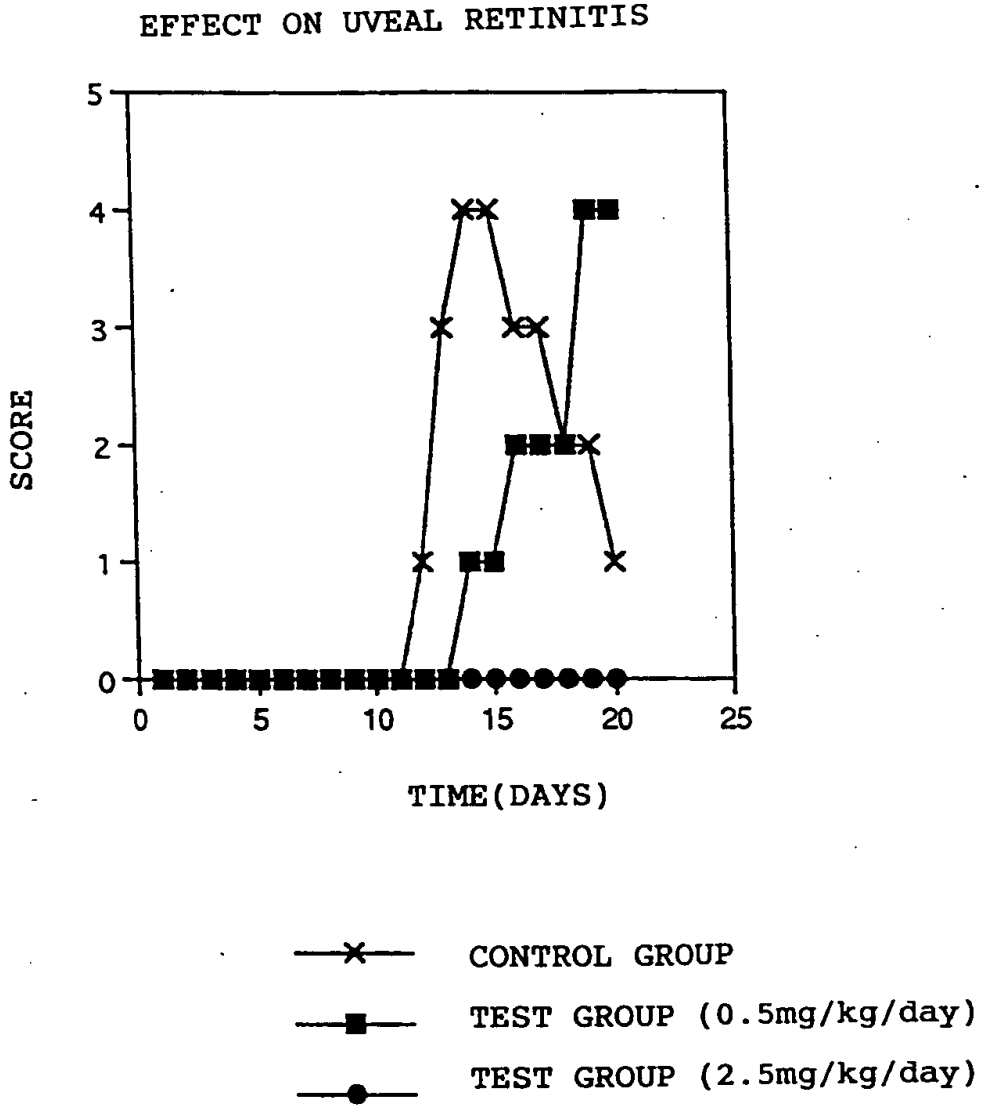
2. Remedies as claimed in Claim 1 characterized by containing, as the active ingredient, one or more compounds represented by the following general formula (II) or salts thereof:



(II)

wherein R_8 and R_9 are the same or different and each represents a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms.

Fig. 1


EFFECT ON UVEAL RETINITIS
SCORE
0
1
2
3
4
5
0
5
10
15
20
25
TIME(DAYS)
CONTROL GROUP
TEST GROUP (0.5mg/kg/day)
TEST GROUP (2.5mg/kg/day)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/00854

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 A61K31/505, C07D475/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 A61K31/505, C07D475/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 6-16558, A (Chugai Pharmaceutical Co., Ltd.), January 25, 1994 (25. 01. 94)(Family: none)	1 - 2
A	JP, 4-352785, A (Chugai Pharmaceutical Co., Ltd.), December 7, 1992 (07. 12. 92) & EP, 543997, A & US, 5354753, A	1 - 2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
May 23, 1997 (23. 05. 97)	June 3, 1997 (03. 06. 97)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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